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OAK RIDGE NATIONAL LABORATORY

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UNION CARBIDE CORPORATION

NUCLEAR DIVISION

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OAK RIDGE, TENNESSEE 37831

OFFICE OF THE DIRECTOR

December 6, 1968

Professor Joshua Lederberg
Stanford University Medical Center
Palo Alto, California

Dear Josh:

It was very kind of you to take the trouble to forward the reference to Dr. Umezawa's work with bleomycin. Fortunately, we were able to obtain copies of several reports from the Japanese reporting on their use of this drug. At the moment Marge is responding surprisingly well to the Cytoxan and Vincristine.

There is another matter that is very much on my mind these days, and on which I would like your opinion. You of course are aware of the L-asparaginase-leukemia story. It now seems that here in Oak Ridge we may have run onto two other neoplasms in which there may also be anomalies in the non-essential amino acid requirement. I refer first to Stanfield Rogers' finding that the Shope papilloma in rabbits has a requirement for arginine; and a very recent finding by Regan, Vodopick, Takeda (from Mie Prefectural University in Tsu, Japan), and Lee at ORNL and at Oak Ridge Associated Universities, that human granulocytic leukemia may have an anomalous requirement for serine.

The second finding strikes some of the experts as being questionable because the granulocytes that should have been used as controls are not available, and therefore comparison was made with normal fibroblasts. Nevertheless, the anomaly in the serine requirement is sufficient to make the thing very suggestive. Coupled with these findings is a very cute invention, again by Stanfield Rogers, for selectively removing specific amino acids from the blood. Rogers runs the subject's blood through an artificial kidney; and on the other side of the dialysis membrane he puts in an enzyme that chops up the unwanted amino acid, but leaves the other blood constituents untouched. In this way he has been able to remove arginine from rabbits (by using arginase); he is now collaborating with a group at Indiana University in removing histidine from children afflicted with histidinemia. Rogers now has several

instances in which he has treated rabbit papilloma with his dialysis technique by reducing the arginine, and he seems to have achieved a significant reduction in the size of the tumors. I enclose before and after pictures of one of the rabbits he treated.

The reason I belabor these points is that I understand from Stan Rogers that shortly after you had done the work on bacterial mutations with Tatum and Beadle you suggested that neoplastic tissues might well be characterized by such metabolic anomalies. I also understand from Rogers that you implied that the time was right to systematically look at the neoplasms with the idea of identifying such metabolic anomalies that conceivably could be attacked by specific agents that would go after the particular anomaly.

It does seem to me that we now have two cases - L-asparagine in leukemia and arginine in Shope papilloma - and possibly a third, serine in granulocytic leukemia, where your conjecture has been proved right and that, with Rogers' dialysis technique, one has a way of going after these anomalies. The question is therefore whether the time is right in your opinion to launch a much larger effort on characterizing tumors, particularly with respect to requirements for specific amino acids and maybe other metabolites. I guess the thing that puzzles me is that this seems like a fairly obvious approach, and one wonders whether this has not been investigated in the past and is now buried in the voluminous biochemical literature.

We are talking about these things here at the Laboratory, and it would be most helpful if you could let me know whether you have any ideas on this subject.

Sincerely yours,

Alvin

AMW:pl

Alvin M. Weinberg

Enclosures